Potential role of 2,2'-biphenylquinones in the carcinogenic/anti-cancer activity of dioxins

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Modes of carcinogenicity for the well-known environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) have been investigated by numerous research groups over the past several decades. Despite several decades of research, "the mechanisms underlying the carcinogenicity of TCDD still remain unclear" (Lin et al., 2007), although it has been postulated that the all of the biological effects from TCDD are believed to be mediated by the aryl hydrocarbon receptor (Hankinson, 1995). Recent work also suggests TCDD may have anti-cancer activity as well (Hsu et al., 2007).

In addition to the potential mechanisms that other groups have put forward to explain the carcinogenic and anti-cancer activity of TCDD, this comment suggests an additional potential pathway to help explain the collective results within the field, and one that has not received any attention among the dioxin research community. Prior work by this author and his colleagues have shown the existence of a novel photochemical mechanism for dioxins (Guan and Wan, 2003, 2004; Rayne et al., 2002, 2005) (Figure 1). In short, dibenzo-*p*-dioxins (**1**) undergo a singlet-state photochemically initiated aryl-ether bond homolysis that yields reactive 2-spiro-6'-cyclohexa-2',4'-dien-1'-one (**2**) and subsequent 2,2'-biphenylquinone (**3**) intermediates. Under steady-state irradiation, the 2,2'-biphenylquinones undergo excited state hydrogen abstraction from the organic solvent to give the corresponding 2,2'-dihydroxybiphenyls. In the absence of continued irradiation, 2,2'-biphenylquinones with electron donating substituents (EDGs) thermally rearrange to corresponding oxepino[2,3-b]benzofurans, whereas the unsubstituted 2,2'-

biphenylquinone and its derivatives with electron withdrawing groups (EWGs) thermally rearrange to corresponding 1-hydroxydibenzofurans. The lifetime of the 2,2'-biphenylquinones prior to the intramolecular rearrangements depends on the nature of the substituents on the cyclohexadienone rings, but typically varies from seconds to several minutes. Collectively, our work showed this mechanism was operative for the unsubstituted parent compound and across a wide range of alkyl, alkoxy, and halogen substituted derivatives, including mono- through octa-chlorinated members and the well-known TCDD, suggesting it may be a general mechanism for dioxins.

An early study found a linear relationship between the photolysis rates and toxicity of various 2,3,7,8-chlorinated dioxins (Mamantov, 1984), which suggested that common pathways - potentially yielding similar biologically active intermediate species - were possible between the photochemical (excited-state) and toxicological mechanisms of this compound class. Supporting evidence for a potential link between the photochemical and toxicological mechanisms of dioxins lies in the well-known formation of DNA adducts by quinones and quinone methides (see, *e.g.*, Freccero, 2004; Wang et al., 2005). Consequently, it is reasonable to propose that 2,2'-biphenylquinones may be active toxicological intermediates from dioxins such as TCDD, and that these intermediates may also play a role in expressing both the carcinogenic and anti-cancer activities reported by various groups (Figure 2).

However, there are no reactivity studies of representative 2,2'-biphenylquinones under physiologically relevant conditions. Our photochemical work was conducted under conditions that promoted subsequent intramolecular thermal rearrangements of the 2,2'-biphenylquinones.

However, *in vivo*, any toxicological mechanisms leading to 2,2'-biphenylquinone formation from dioxins in the proximity of DNA may result in adduct formation. The broader research community is encouraged to consider this potential new mechanism for dioxin toxicology in the design of future studies, the positive or negative findings from which will nicely supplement the strong datasets developed by previous and current research groups.

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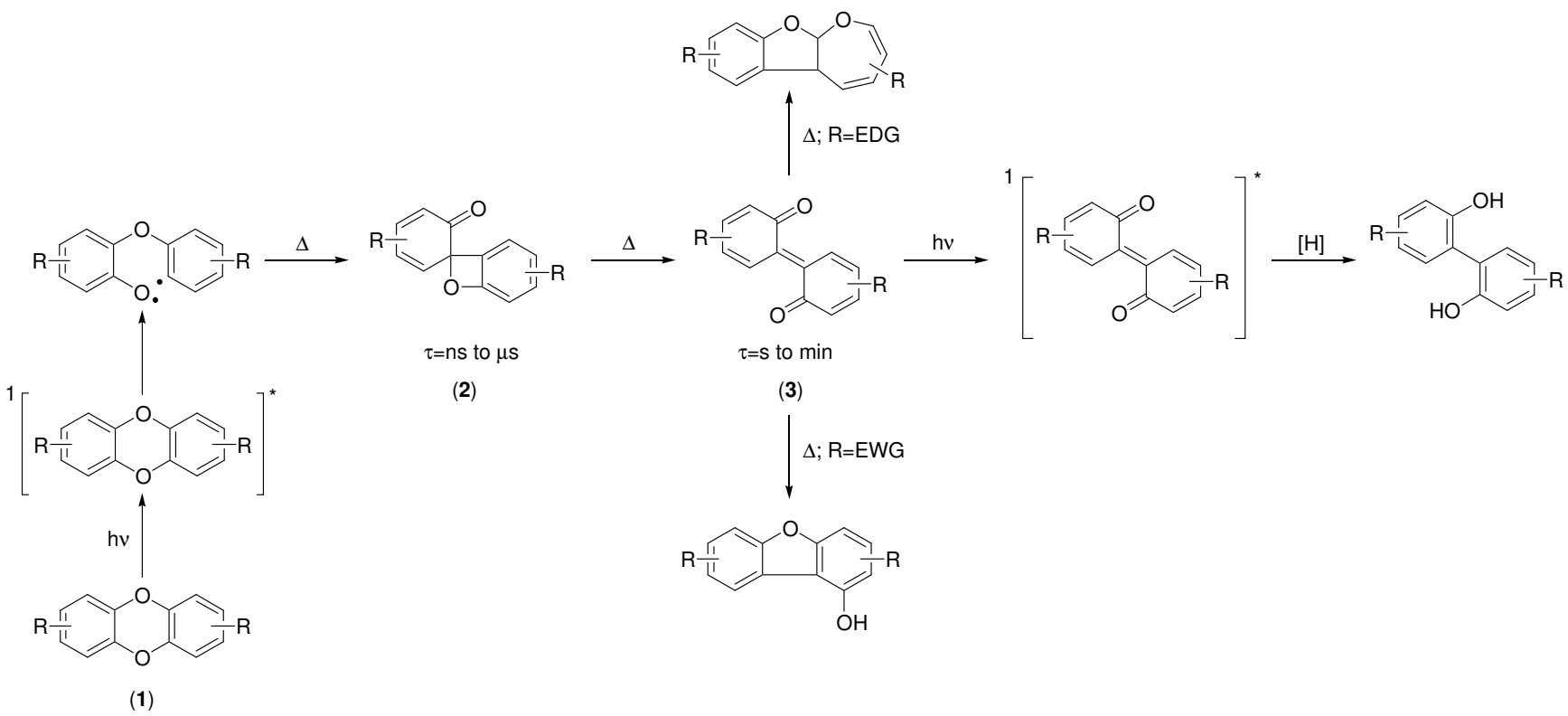

Figure 1. Proposed photochemical mechanism for dioxins.

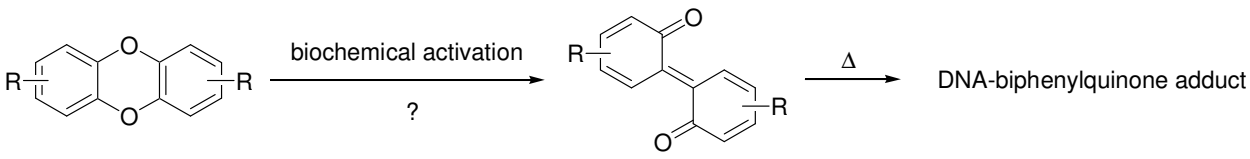

Figure 2. Proposed biochemical activation of dioxins and subsequent thermal reaction of 2,2'-biphenylquinones with DNA.